IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: OKAMURA=2B

In re Application of:	)	Art Unit: 1646
H. OKAMURA et al.	)	Examiner: D. Jiang
Appln. No.: 09/050,249	)	Washington, D.C.
Date Filed: March 30, 1998	)	Confirmation No. 6601
For: IFN-GAMMA PRODUCTION INDUCING PROTEIN…	)	

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner for Patents
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Sir:

I, Haruki OKAMURA, declare and state as follows:

1. I am a citizen of Japan residing at Nakahozumi, 2-12-32, Ibaraki-shi, Osaka, Japan.

2. I graduated from Osaka University, Faculty of Science (Biology) and received a Doctorate of Science from Osaka University in 1976.

3. I have been working for Hyogo College of Medicine since 1976, where I am the professor of the Laboratory of Host Defenses, Institute for Advanced Medical Science.

4. I have been actively engaged in research in the field of microorganisms and cytokines, particularly mouse and human

interleukin-18 (IL-18). A copy of my curriculum vitae is attached hereto.

5. I am one of the inventors named in the above-identified patent application (hereinafter designated as "instant application") and I am thoroughly familiar with the original specification of the instant application and the presently claimed invention.

6. I understand that the examiner takes the position that the present claims are obvious/unpatentable over Nakamura et al., "Purification of a Factor which Provides a Costimulatory Signal for Gamma Interferon Production", *Infection and Immunity*, 61(1):64-70 (1993), a publication in which I am a co-author and which is hereinafter referred to as Nakamura et al. I am also thoroughly familiar with the disclosures of this publication and I hereby declare that Nakamura et al. cannot make obvious the presently claimed invention for the reasons below:

7. Summary of Nakamura et al. and relationship between Nakamura et al. and Okamura et al.

As reported in Nakamura et al., I and my co-authors found a protein factor in mouse sera, which induces a high level of interferon-γ (IFN-γ) production in the presence of interleukin-2 (IL-2), monoclonal anti-CD3 antibody (anti-CD3 MAb), or concanavalin A (ConA), and which has the following properties:

i) The molecular weight of the protein factor was much smaller by SDS-PAGE (50 to 55 kDa) than by the molecular sieve technique (70 to 75 kDa); and

ii) When electrophoresed on SDS-PAGE to give an apparently single protein band with a molecular size of 50 to 55 kDa, the factor lost its IFN-γ-inducing activity.

When the apparent molecular weight of the active form of a conventionally known natural killer stimulatory factor, i.e., 75 kDa NKSF/interleukin-12 (IL-12), its IFN-γ inducibility, and the synergy of IL-12, anti-CD3 MAb, or a mitogenic lectin were all found to be similar to those of the factor in Nakamura et al., I and my co-authors speculated that the factor may possibly be the natural killer stimulatory factor NKSF/IL-12. However, we could not provide proof because we were unable to obtain the factor in an isolated and purified form and in sufficient yield necessary for identifying it as either a novel substance or the natural killer stimulatory factor NKSF/IL-12.

To overcome this problem, we tried to isolate cells that produce this factor in order to facilitate the isolation and purification of the factor in a sufficient yield to perform further analysis. We screened cells, such as from established macrophage cell lines, as potential candidate cells that sufficiently express the factor. Nevertheless, despite our best efforts, we were

unsuccessful in obtaining such cells, and our research in this regard made not the slightest bit of progress.

Following the studies reported in Nakamura et al., I and my co-authors of Okamura et al., *Infection and Immunity*, "A Novel Costimulatory Factor for Gamma Interferon Induction Found in the Livers of Mice Causes Endotoxic Shock", 63(10):3966-3972 (1995), hereinafter referred to as Okamura et al., which was published after the filing date of the instant application, continued to study on how to establish the identity of the factor in Nakamura et al. and perform further analysis. For this purpose, we extensively screened cells which induce the factor from Nakamura et al.

As a result of these later studies, we unexpectedly discovered that mouse liver cells produce a substance that induces IFN-γ production and named it IGIF (Interferon-Gamma Inducing Factor). To discern the relationship between the factor from Nakamura et al. and the IGIF from Okamura et al., we re-prepared Nakamura et al's factor for comparison with IGIF. The re-prepared factor exhibited an IFN-γ-inducing activity in a protein species with a molecular weight of 19 kDa in addition to the one with a molecular weight of 75 to 80 kDa by molecular sieving in the presence of dithiothreitol (DTT). The activity of inducing INF-γ production, however, was observed only in the molecular species of 75 to 80 kDa in the absence of DTT. Moreover, the protein species

with a molecular weight of 75 to 80 kDa was reduced to 19 kDa on 0.1% SDS-polyacrylamide gels in the presence of DTT. In addition, the NH_2-terminal amino acid sequence of the re-prepared factor was determined to be the same as that of IGIF purified from mouse liver extracts. Based on these results, I and my co-authors of Okamura et al. concluded that "*The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF.*"

8. Difficulty of obtaining the monoclonal antibody of the instant application based on Nakamura et al.

As stated above, at the time Nakamura et al. was published, I and my co-authors of Nakamura et al. had neither isolated the factor in an isolated and purified form nor identified the factor as a novel substance (even if the factor contained the IGIF later identified in Okamura et al.), and we even speculated that the factor may be the NKSF/interleukin-12 (IL-12) that induces IFN-γ production.

I hereby declare that, under these circumstances, no researcher would have considered preparing any monoclonal antibody to the factor because, first of all, I and my co-authors had not established a method in Nakamura et al. for providing sufficient amounts of the factor necessary for preparing such a monoclonal antibody. Second of all, even if monoclonal antibodies were to be obtained using the factor, nobody could have selected the desired monoclonal antibody to the factor from among the various

antibodies to the factor or possible NKSF/interleukin-12 (IL-12) present in the same protein band or fraction.

I further declare that I and my co-authors of Nakamura et al. did indeed need sufficient amounts of the factor from a source other than mouse sera in order to discern the identity of the factor; however, we were unable to establish such technique and to obtain sufficient amounts of the factor at the time.

9. Breakthrough

I and my co-inventors in the instant application consistently and diligently continued studying the factor of Nakamura et al. and, prior to the publication of Okamura et al., we found that mouse liver cells produce a mouse interleukin-18 (mIL-18) corresponding to the IGIF in Okamura et al. (hereinafter designated as "mIL-18/IGIF") and serve as a cell source for mIL-18/IGIF and we established a technique for producing sufficient amounts of mIL-18/IGIF necessary for preparing the monoclonal antibody of the instant application using recombinant DNA technology with mRNA isolated from mouse liver cells as mIL-18/IGIF-producing cells.

I declare that the above finding was the breakthrough or the key to success for obtaining the monoclonal antibody of the instant application and this is evidenced by the disclosure of Okamura et al., at page 3972, left column, lines 12 to 15:

> ***The complementary DNA for the IGIF*** *has recently been cloned (unpublished data). This will enable a*

> *sufficient supply of recombinant IGIF or* ***the antibody against it*** *for examination of its biological actions.* (emphasis added)

I further declare that, without the above finding, one of ordinary skill in the art could never have succeeded in arriving at the monoclonal antibody of the instant application based on Nakamura et al. because the prior art and the knowledge of those of ordinary skill in the art lacked the above-mention key to success. Consequently, Nakamura cannot lead one of ordinary skill in the art to the presently claimed invention.

10. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Sep, 16 2009
Date: September 16, 2009

Haruki Okamura
Haruki OKAMURA

Attachment:
Exhibit A: Curriculum vitae of Haruki OKAMURA

CURRICULUM VITAE

Dr. Haruki OKAMURA
Nakahozumi, 2-12-32, Ibaraki-shi,
Osaka, Japan

PERSONAL: Japanese Citizen
Married

EDUCATION:

1970	Graduated from Osaka University, Faculty of Science (Biology)
1976	Degree of Ph. D, Osaka University
1976	Scholarship Student, Institute for Microbial Diseases, Department of Measles, Osaka University

BRIEF CHRONOLOGY OF EMPLOYMENT:

1976	Assistant Professor, Department of Bacteriology, Hyogo College of Medicine
1997-1999	Associate Professor, Laboratory of Host Defenses, Institute for Advanced Medical Science, Hyogo College of Medicine
1999-	Professor, Laboratory Host Defenses, Institute for Advanced Medical Science, Hyogo College of Medicine

SOCIETIES:

Society of Immunology Japan
Society of Interferon and Cytokine Japan, Manager
Society of Inflammation Japan

PUBLICATION LIST
(Dr. Haruki OKAMURA)

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